

Risk analysis systems for veterinary biologicals: a regulator's tool box

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Summary: Recent advances in biology and technology have significantly improved our ability to produce veterinary biologicals of high purity, efficacy and safety, virtually anywhere in the world. At the same time, increasing trade and comprehensive trade agreements, such as the Uruguay Round of the General Agreement on Tariffs and Trade (GATT: now the World Trade Organisation [WTO]), have put pressure on governments to use scientific principles in the regulation of trade for a wide range of products, including veterinary biologicals. In many cases, however, nations have been reluctant to allow the movement of veterinary biologicals, due to the perceived threat of importing an exotic disease.

This paper discusses the history of risk analysis as a decision support tool and provides examples of how this tool may be used in a science-based regulatory system for veterinary biologicals. A wide variety of tools are described, including qualitative, semi-quantitative and quantitative methods, most with a long history of use in engineering and the health and environmental sciences.

KEYWORDS: Fault tree analysis – Generic process – Risk analysis – Scenario tree analysis.

INTRODUCTION

In order to make regulatory decisions which may be justified scientifically, governments and industry need a common set of methods and technologies for determining the potential risks associated with imported veterinary biologicals. Risk assessment provides such a decision support system. Risk assessment is the science of understanding hazards or accidents, the likelihood that they will occur, and the magnitude of the consequences if they do occur. Risk assessment makes use of facts from virtually all biological and engineering sciences: epidemiology, pathology, virology and bacteriology, physiology, geography, chemistry, materials science, etc. The facts are

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organized into structured predictive models which can be analyzed and agreed on by interested parties. Most importantly, risk assessment methods can help to produce transparent, consistent and well-documented decisions which are able to evolve as new scientific information emerges. This paper is designed to provide regulators and other interested parties with a brief overview of risk assessment and the concepts behind it, and to illustrate how risk assessment applies to veterinary biologicals.

There are many methods of risk assessment. For many years, a variety of risk assessment methods have been used by engineers, financial analysts, insurance companies, economists and others. These methods comprise a broad range of powerful tools which can be used to develop a valid risk assessment for products of animal origin in international trade, including veterinary biologicals. These methods are the tools by which the risk assessor accomplishes the task at hand. The large number of tools suggests that the risk assessor has an extensive tool box from which to select the most appropriate tool for the job.

The tool analogy is a powerful one. For example, if one wishes to build a house, a hammer alone is insufficient. The carpenter may require a saw, a screwdriver and a 'plumb bob', among other tools. A more complex job may require a level, electrically-powered tools and other more sophisticated tools. Regardless of the level of sophistication, the tool used must be appropriate for the job at hand. A saw is a poor choice if the job is to push a nail through two pieces of wood. In general, simple tools will be more useful than sophisticated, specialized tools. However, there is usually more than one tool which can be used to accomplish a task. The selection must rely on common sense, experience and the needs of the decision-makers and other interested parties. These needs must then be balanced against the resources and time available.

For risk assessment tools to be applied effectively in the regulation of veterinary biologicals, it is important that both regulators and the regulated community understand the history of risk assessment and the terminology involved. Many nations will eventually find themselves using these techniques and, to ensure that the techniques are used consistently, all parties must use a common vocabulary. The following sections contain a discussion of the historical development of risk assessment as a decision tool, as well as definitions of several key terms and concepts used in risk assessments, an overview of the risk assessment process, and descriptions of several risk assessment methods.

HISTORICAL PERSPECTIVE

The science of risk analysis grew out of early efforts in the aeronautics and (later) aerospace industries to understand the failure of aircraft. After the First World War, as the level of air traffic and the frequency of air crashes increased, government and industry needed ways to evaluate reliability, to understand the effects of equipment failure and to set reliability criteria. During the 1940s, Robert Lusser, a mathematician working on the German missile programme, developed the product law of series components to explain the failure of V-1 rockets (1). This law states that the reliability of a 'series' system is equal to the product of the reliabilities of the components of the system. Thus, in a series system, the reliability of the individual components must be much higher than the overall system reliability required for acceptable performance. This law is fundamental to the development of risk assessments for man-made systems, including those used to develop and manufacture veterinary biologicals.

Techniques for analyzing the reliability of machines progressed in the 1950s and 1960s, as engineers studied more complex systems, including nuclear power plants and spacecraft. During this time period, engineers first began using a method for logically and systematically describing the circumstances under which a system could fail. This method, called 'fault tree analysis', was originated by H.A. Watson to evaluate the safety of a launch control system (8). D.F. Haasl further developed fault tree construction and expanded its use to the solution of a wide variety of industrial safety and reliability problems (4). Concurrently, efforts to understand the effects of sequenced events led to the development of 'event tree analysis' and 'probability scenario analysis' (PSA). This latter technique is based on the 'game theory' studies of the three mathematicians who won the Nobel Prize for Economics in 1994. H. Kahn used game theory and its precepts to evaluate the 'What if?' scenarios of nuclear proliferation (2). The method quickly gained acceptance in financial analysis, engineering applications and general economic evaluations.

Responding to concerns about the health effects of toxic chemicals, scientists began to apply formal risk assessment techniques in the biological sciences during the late 1960s and early 1970s. Biological systems were not well understood, and the methods therefore employed highly conservative models and default assumptions to ensure that human health was protected.

The use of these techniques should now be expanded to the regulation of veterinary biologicals, to ensure that the benefits of veterinary medical sciences are felt by as many nations as possible. In fact, this expansion is required by the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) and the new World Trade Organization (WTO). Under the WTO system, nations are expected to regulate the movement of veterinary biologicals on the basis of a scientific assessment of the risks involved. A clear understanding of the tools and techniques available to assess the risks associated with veterinary biologicals will therefore serve to enhance trade and reduce inappropriate or illegal non-tariff trade barriers. The Office International des Epizooties is recognized by the WTO as the primary organization for setting standards in risk assessments for animals and animal products.

DEFINITIONS AND CONCEPTS

The following terms and concepts are important to the understanding of risk assessment:

- **Consequence analysis:** the evaluation of effects of incident outcomes independent of frequency or probability. An undesirable consequence is known as 'damage' or 'harm'.
- **Hazard:** a source of risk and, in this instance, a substance or action which may cause harm.
- **Quantitative risk analysis:** the systematic development of numerical estimates of expected frequency and/or consequences of potential events.
- **Risk:** the likelihood (probability) and magnitude (severity) of the occurrence of an adverse event.
- **Safeguard or mitigation:** a process or action undertaken to reduce the risk associated with a given hazard.

Two basic concepts in risk analysis are also relevant to veterinary biologicals: the relationship between risk and hazard, and the distinction between risk and uncertainty.

Risk vs. hazard

The first important concept to be understood is the distinction between risk and hazard. A hazard is usually defined as a source of danger, injury or damage. The definition of risk, however, usually includes the probability or likelihood that damage or injury will actually occur, and the magnitude or severity of an undesired event. With this qualitative definition in mind, it is useful to state this relationship in the following symbolic equation:

$$\text{risk} = \frac{\text{hazard}}{\text{safeguard}} \text{ or } R = \frac{H}{S}$$

Looking at this relationship, it is clear that a large hazard and a small safeguard yield a large risk, while increasing the size of the safeguard reduces risk. It is also apparent that, unless the hazard (H) is zero, there is always an associated risk.

Following the product law of series components, risks from a series of events are multiplicative, as follows:

$$R_{\text{total}} = R_1 \times R_2 \times R_3 = \frac{H_1}{S_1} \times \frac{H_2}{S_2} \times \frac{H_3}{S_3}$$

Thus, in a system for producing veterinary biologicals, each event in a scenario has a given probability of occurrence. This leads to two important observations. Firstly, high risk events in a scenario can be identified and, if appropriate, reduced. Secondly, it becomes possible to identify data needs if decision-makers require reduced uncertainty before making a decision.

Risk vs. uncertainty

The concept of risk involves uncertainty in both the likelihood and magnitude of the consequences. Reducing the amount of uncertainty regarding either the likelihood of an adverse event or the magnitude of the consequences does not necessarily change the actual risk. However, reducing the uncertainty does give a more precise evaluation of the risk. In the case of veterinary biologicals, it is theoretically possible for a product to be contaminated with a host-specific virus. If the product is intended for use in a susceptible species, there is a high probability with low uncertainty of a major adverse event. However, if the product is intended for a non-susceptible species, there may be a small risk with a high level of uncertainty of a major adverse event.

UNDERSTANDING THE RISK ASSESSMENT PROCESS

Risk assessment is a process. For the process to work most effectively, it must have the following attributes:

- a well-defined goal or set of goals
- a common set of tools
- an appropriately-documented and transparent risk assessment.

It is important for the decision-maker – as well as the individuals involved in preparing the risk assessment – to understand the reason for performing the risk assessment and the goals of the exercise. Decision-makers must take an active role in the process and must articulate their concerns and questions as the goals are developed. Moreover, as the risk assessment process proceeds, the risk assessor must communicate with the decision-maker if new information or insights may affect the goals of the assessment.

Important reasons for performing a risk assessment include the following:

- to support a decision to issue or deny an approval or import permit for a product
- to evaluate a specific agent or hazard
- to evaluate a geographic region
- to inform policy discussions.

Depending on the hazards involved, the degree of detail required and the underlying reason for the assessment, the tools selected will vary. The selection of tools will also be determined by the information and data available, resource and time constraints, and whether the assessment is initial or final.

Risk assessments must be transparent and appropriately documented. The goals of the assessment should be explicitly stated, all appropriate hazards identified, the methods used declared, and all assumptions and uncertainties described, as appropriate. The documentation must provide the information needed to communicate the logical basis for the decision and facilitate the risk communication process between the decision-maker, the regulated party and the general public. Finally, just as the depth of the assessment must reflect the nature and significance of the decision, the documentation should accurately reflect the risk assessment performed.

Risk assessments are frequently iterative. As the risk assessment process is affected by realistic limits on time and resources, an improving knowledge base and changing societal needs, a risk assessment completed today may not be adequate six months from now. A transparent, well-constructed and well-documented risk assessment will facilitate the inclusion of new scientific information and provide improved support for any new decisions required.

RISK ASSESSMENT TOOLS

As noted above, there are many methods and techniques for conducting risk assessments. In general, these techniques can be classified in one of three groups: qualitative, semi-quantitative or quantitative. Qualitative techniques are most commonly used in cases where there appears to be limited risk, where data of sufficient quality are extremely limited, or where there are large amounts of data relevant to a very complex question. Semi-quantitative methods are useful in cases where there is a need to reduce uncertainty but where data are limited, or where there are complex questions. Quantitative methods are most useful for situations where a small number of hazards are involved.

For veterinary biologicals, semi-quantitative methods may be useful, for example, in examining a complex set of questions involving a genetically-modified virus. However, practical management considerations may make the quantitative method more useful for characterizing the risk of contamination of a vaccine by only one or two specific pathogens.

An initial 'screening' risk assessment is often undertaken to determine the need and data requirements for a more comprehensive risk assessment, and to test the appropriateness of the selected method for the question or questions involved. In many instances, qualitative or semi-quantitative assessments are used to determine data requirements for a more comprehensive quantitative assessment. One or more methods may be examined to determine which 'tool' is best for the situation.

During the 1990s, a number of risk assessment techniques have been developed and used by veterinary regulatory authorities around the world. Many of these techniques are described in detail in this issue of the *Review*. It is important to note, however, that the chosen tool must provide useful answers to the questions at hand. Only the active participation of the risk assessor, the risk manager (regulator) and the regulated community can ensure that the proper questions are asked in the risk assessment process.

Qualitative and semi-quantitative methods

A brief description is given below of several methods used by regulators to assess the risks associated with a variety of products, including veterinary biologicals. This is not an all-inclusive listing, but should provide a good overview of the tools available.

Decision sheet

The decision sheet is a compilation and organization of the information available concerning a proposed action. The sheet contains a description of the proposed action and a concise description of the hazards being evaluated. Additionally, the sheet could include information concerning geography, manufacturing techniques, target species, incidental hosts, and other information or supporting discussion, as appropriate. This is the simplest system for organizing the available information for the decision-maker. The decision sheet contains qualitative information which can be applied systematically, to some extent, and is often a useful starting point for a more in-depth analysis. Nevertheless, in some instances, it will provide the decision-maker with the information required to proceed.

Generic process

The 'generic process' is flexible and adaptable to a number of situations. It was originally developed as a method to evaluate the risks associated with the importation of plants or plant commodities (6). This method requires the risk assessor to answer sequentially a standard set of questions about each product. It may be used in one of the following ways:

- qualitatively (with risk ranking of high, medium or low)
- qualitatively (with ordinal ranking of risk, e.g. high = 10, low = 1)
- semi-quantitatively (with numerical estimates of risk for each element in the model).

The 'generic process' can be completed relatively quickly, usually makes relatively little demand on resources, and can be documented. This process can therefore provide the decision-maker, the regulated community and the public with the background material needed to make decisions and choose options. The method is presented at length by Gay and Orr (3) and Roth *et al.* (7).

Enhanced hazard identification

The method of 'enhanced hazard identification' (5) evaluates an established set of criteria for the proposed action (e.g. importation of a veterinary biological).

Evaluations are translated into ordinal rankings which can yield relative risk rankings. If enough criteria are carefully selected and properly evaluated, and the analysis is adequately documented, this method can reveal a fairly comprehensive picture of the risks associated with a proposed approval or importation. The primary strength of this method is that it provides a highly systematic evaluation of criteria, which can be applied to many different products. The major weakness is that the actual probability of an accident cannot be determined.

Quantitative methods

Worst-case scenario development

This method utilizes a worst-case scenario to establish that a given action is either extremely improbable or within the bounds of acceptable risk. Each point at which an adverse event may occur is identified and is assigned a numerical value. The final worst-case probability of the accident is then calculated. Like the generic process, this method can be completed quickly, is not resource-intensive and can be documented. Moreover, it has the advantage of being fully quantitative, and new information can therefore be quickly incorporated. Unfortunately, this method can become difficult to use if several hazards must be evaluated. The example presented below (R.H. Kimberlin, personal communication) illustrates a worst-case scenario for infection with the agent bovine spongiform encephalopathy (BSE) in a master seed exposed to bovine serum in the United Kingdom.

Total volume of serum used	$= 3.5 \times 10^2 \text{ ml}$
BSE infectivity in serum	$= 1.0 \text{ i.e. } 50\% \text{ lethal dose (LD}_{50})/\text{ml}$
Incidence of BSE in the United Kingdom	$= 10^{-1}$
Maximum contamination in the serum	$= A \times B \times C = 3.5 \times 10^1 \text{ i.e. LD}_{50}$
Relative efficiency of the intramuscular route	$= 10^{-2}$
Effective contamination	$= 3.5 \times 10^1 \text{ i.e. LD}_{50} \times 10^{-2}$ $= 3.5 \times 10^{-1} \text{ i.e. LD}_{50}$
Proportion of master seed virus in a single dose of vaccine	$= 6.4 \times 10^{-13}$
Maximum exposure in a single dose of vaccine	$= \text{effective contamination} \times \text{proportion of the master seed virus}$ $= 3.5 \times 10^{-1} \text{ i.e. LD}_{50} \times 6.4 \times 10^{-13}$ $= 2.2 \times 10^{-13} \text{ LD}_{50} \text{ units/dose}$
50% chance of a single dose of vaccine producing BSE	$= (2.2 \times 10^{-13})^{-1}$ $= 4.5 \times 10^{12}$

This example shows that there is a 50% chance of one dose in 4.5 trillion producing BSE; i.e. the probability of a dose of vaccine producing a case of BSE is one in nine trillion.

Probability scenario analysis

This method is based on 'event tree analysis'. PSA identifies the hazard involved, describes an initiating event, and then details the possible sequences which may lead to an accident. For each point on the pathway where a new event occurs, precise questions are asked. A given initiating event may have several branching pathways, each providing separate end-points. The overall probability is the total of the probabilities in each of these branches. The scenario tree provides a systematic means of recording potential accident sequences and defining the relationships between the initiating events and subsequent events which result in accidents.

When all branches of the scenario tree have been developed, the data contained in the model are quantified. The model can be used with various kinds of data. For example, a sophisticated epidemiological survey may provide a mean and a standard deviation (SD) for a given event. This information, both mean and SD, can be used directly at one point in the model. At another point along a branch, data may be more limited and are presented as a simple three-point curve or probability distribution function (PDF), with the three points being the 'most likely' estimate, and the highest and lowest values consistent with the evidence available. This spread gives convincing clarity for estimates, as the uncertainty of each estimate is displayed as part of the PDF. When the highest and lowest values are close to each other, this indicates a relatively high degree of certainty regarding an estimate, just as a small SD indicates greater certainty than a large SD. The probability for any given scenario is then calculated as the product of the events in the scenario. Figure 1 shows an example of a portion of a scenario tree for the risks associated with the production of a conventional veterinary biological.

For each point on a branching pathway, data are carefully collected and summarized. At each point, the evidence used to develop the quantitative estimate at that point must be displayed, and the reference(s) from which the evidence was obtained must be provided. This careful step-by-step analysis and point-by-point documentation leads to the development of probability estimates which may be extremely useful to decision-makers. Arguments about end-points can be re-directed to discussions about the evidence: Is different evidence available from that used in the model? Was the evidence used appropriately? As new or different evidence is uncovered, it can be placed in the model and the simulation re-run to provide an updated estimate of probability. This process, along with the general availability of computerized spreadsheets and simulation software, greatly improves the flexibility of this method. There can be no charges of secrecy, for a properly-documented PSA risk assessment will display the model and all the facts used in the model to develop the probability estimate. If well-organized and carefully written, the document will be transparent to interested lay readers as well as health professionals. Unlike less quantitative risk assessment methods, this method limits the use of value judgements, provides a clear view of the uncertainties involved, and promotes the development of consistent and scientifically-justifiable decisions.

The primary limitation associated with PSA is that the method tends to require more data and resources than other methods. The scenario trees themselves must be carefully developed and validated, and the available data collected and analyzed. If the risks involved appear to be limited, if there is little or no data available, or if there are a large number of hazards which must be evaluated simultaneously, the generic process or some other less quantitative tool may be more useful. Nevertheless, regulators and the regulated parties must understand that this method can provide great insights into the

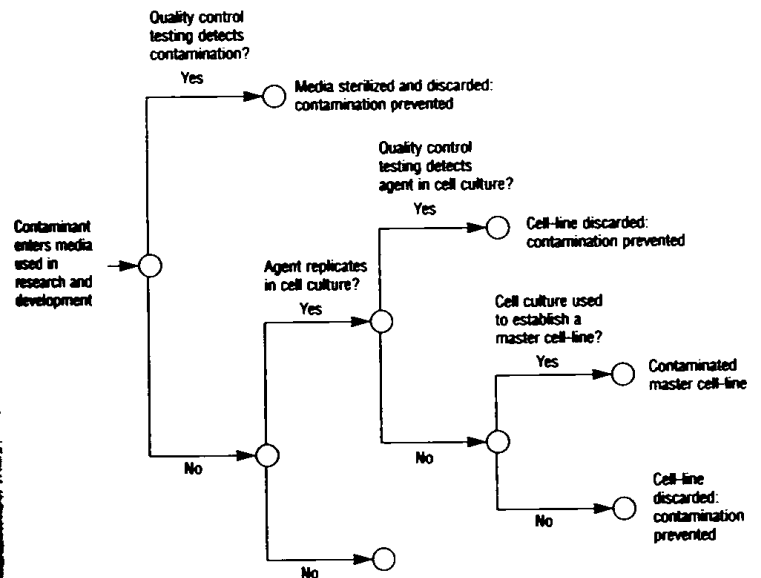


FIG. 1

Example of part of a scenario tree analysis for risks associated with the production of veterinary biologicals

potential risks associated with the movement of veterinary biologicals in international commerce, and it is likely to become the global standard for a comprehensive risk assessment.

CONCLUSIONS

The possibility that a veterinary biological manufactured in a foreign country could carry an exotic animal disease has greatly inhibited the free movement of these products in international trade. The application of a wide range of risk assessment techniques will allow regulatory authorities, regulated parties and the interested public to manage successfully the production and movement of these important health products throughout the world. In the majority of cases, the generic process or some other semi-quantitative risk assessment technique will be the tool of choice for evaluating veterinary biologicals in international trade. In some cases, however, where the potential risks are large or great uncertainty exists, a quantitative technique such as PSA will be the tool of choice.

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LES MÉTHODES D'ANALYSE DES RISQUES APPLICABLES AUX PRODUITS BIOLOGIQUES À USAGE VÉTÉRINAIRE DANS LE CADRE RÉGLEMENTAIRE. – C.G. Osborne, M.D. McElvaine, A.S. Ahl et J.W. Glosser.

Résumé : Grâce aux progrès de la biologie et de la technologie, nous sommes aujourd'hui bien mieux armés que par le passé pour offrir presque partout dans le monde des produits biologiques à usage vétérinaire qui soient garantis purs, efficaces et sans danger. Par ailleurs, l'accroissement des échanges et les accords commerciaux globaux, tels que les négociations d'Uruguay de l'Accord général sur les tarifs douaniers et le commerce (GATT, aujourd'hui l'Organisation mondiale du commerce : OMC), font désormais obligation aux pouvoirs publics de se fonder sur des principes scientifiques lors de la réglementation des échanges d'une large gamme de produits, dont les produits biologiques à usage vétérinaire. Nombre de pays, cependant, hésitent à autoriser la libre circulation de ce type de produits, craignant d'introduire en même temps des maladies exotiques.

Les auteurs retracent l'évolution de l'analyse des risques en tant qu'outil d'aide à la décision et donnent quelques exemples montrant comment l'utiliser dans le cadre d'une réglementation des produits biologiques à usage vétérinaire fondée sur des principes scientifiques. Ils décrivent plusieurs de ces outils, notamment les méthodes qualitative, semi-quantitative et quantitative, dont la plupart sont utilisées depuis longtemps dans les domaines de l'industrie, de la santé et de l'environnement.

MOTS-CLÉS : Analyse des risques – Analyse par « arbre de défaillance » – Analyse par « arbre de scénario » – Procédé générique.

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SISTEMAS DE ANÁLISIS DE RIESGOS DE PRODUCTOS BIOLÓGICOS VETERINARIOS: UNA CAJA DE HERRAMIENTAS PARA EL RESPONSABLE DE LA REGLAMENTACIÓN. – C.G. Osborne, M.D. McElvaine, A.S. Ahl y J.W. Glosser.

Resumen: Los recientes progresos de la biología y la tecnología se han traducido en una sensible mejora de nuestras aptitudes para producir agentes biológicos de gran pureza, eficacia e inocuidad en prácticamente cualquier lugar del mundo. Al mismo tiempo, el incremento del comercio y la existencia de tratados comerciales globales, como la Ronda Uruguay del Acuerdo general sobre Aranceles aduaneros y Comercio (GATT, ahora Organización Mundial del Comercio: OMC), han inducido a los gobiernos a utilizar criterios científicos en la reglamentación de los intercambios comerciales de una amplia gama de productos, entre ellos los productos biológicos de uso veterinario. En muchos casos, sin embargo, y debido al posible riesgo de importar una enfermedad exótica, los países se han mostrado reticentes a autorizar el movimiento de productos biológicos.

Los autores examinan la historia del análisis de riesgos en tanto que instrumento de ayuda a la toma de decisiones, y ofrecen algunos ejemplos sobre la forma en que puede emplearse esta herramienta en el marco de un sistema de reglamentación de los productos biológicos veterinarios basado en criterios científicos. Describen una gran variedad de instrumentos, entre los que figuran métodos cualitativos, semi-cuantitativos y cuantitativos y que poseen, en su mayoría, una larga historia de utilización en los ámbitos de la ingeniería, la salud y el medio ambiente.

PALABRAS CLAVE: Análisis de riesgos – Análisis por árbol de errores – Análisis por árbol de situaciones hipotéticas – Proceso genérico.

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REFERENCES

1. CHORAFAS D.N. (1960). – Statistical processes and reliability engineering. Van Nostrand Reinhold Co., Princeton, New Jersey, 438 pp.
2. COOKE R.M. (1991). – Experts in uncertainty: opinions and subjective probability in science. Oxford University Press, New York, 321 pp.
3. GAY C.G. & ORR R. (1993). – Risk assessment for veterinary biologics of genetically engineered origin. United States Department of Agriculture, Animal and Plant Health Inspection Service. Policy and Program Development Report, Riverdale, Maryland, 36 pp.
4. HENLEY E.J. & LYNN J. (eds) (1976). – Generic techniques in systems reliability assessment. Proc. NATO Advanced Study Institute on Generic Techniques in Systems Reliability Assessment. The University of Liverpool, United Kingdom, 17-28 July 1973. Noordhoff International, Leyden, The Netherlands, 493 pp.
5. ORR R. (1992). – Pest assessment on Australian Riverland citrus. United States Department of Agriculture, Animal and Plant Health Inspection Service, Riverdale, Maryland, 38 pp.
6. ORR R., COHEN S. & GRIFFIN R.L. (1993). – The generic process for pest risk assessment. United States Department of Agriculture, Animal and Plant Health Inspection Service, Policy and Program Development Report, Riverdale, Maryland, 40 pp.
7. ROTH H.J., GAY C.G. & ESPESETH D.A. (1995). – Risk analysis for the importation of veterinary biologicals into the United States of America. In Risk assessment for veterinary biologicals (E.G.S. Osborne & J.W. Glosser, eds). *Rev. sci. tech. Off. int. Epiz.*, 14 (4), 1061-1072.
8. SHOOMAN M.L. (1968). – Probabilistic reliability: an engineering approach. McGraw Hill Book Co., New York, 524 pp.